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EDITORIAL COMMENT

The Role of the Cardiologist in the Primary Prevention of Cardiovascular Disease With Aspirin*

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The fact that blood coagulation plays a role in the pathogenesis of acute vascular disease has resulted in a large number of clinical trials on the effectiveness of antiplatelet drugs, including aspirin, in cardiovascular disease (CVD) (1). Acute myocardial infarction (MI) is generally associated with partial or complete thrombotic occlusion of 1 of the coronary arteries. Both fibrin and platelets are involved in the formation of thrombi. Because recently formed thrombi are mainly composed of fibrin and aggregated platelets, vasoactive mediators such as thromboxane A_2 released from platelets may occlude coronary vessels. It has therefore been suggested that antiplatelet drugs may be active in the primary prevention of MI. Indeed, in a retrospective study involving 473 patients treated with aspirin for rheumatoid arthritis, the drug seemed to reduce the incidence of MI, angina pectoris, sudden death, and cerebral infarction (2). Therefore, antiplatelet therapy looks attractive in the primary prevention of CVD.

BENEFIT AND RISK OF ASPIRIN IN THE PRIMARY PREVENTION OF ACUTE MI

The efficacy and safety of aspirin in the primary prevention of MI have been studied in 6 large-scale trials including a total 660,000 person-years in >95,000 subjects, as noted in a collaborative meta-analysis (3) and put into perspective in a recent review (4). Major coronary events (coronary heart disease mortality and nonfatal MI) are reduced by 18% with aspirin but at the cost of an increase of 54% in major extracranial bleeding. For every 2 major coronary events shown to be prevented by prophylactic aspirin, they occur at the cost of 1 major extracranial bleed (3). Primary prevention with aspirin is widely applied, however. This regimen is used not only because of its cardioprotection but also because there is increasing evidence of chemoprotection of aspirin against cancer (5).

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In this issue of the *Journal,* Hira et al. (6) present the results of a prospective study from the National Cardiovascular Disease Registry's Practice Innovation and Clinical Excellence registry on the inappropriate use of aspirin in primary prevention in nearly 69,000 patients from 119 practices in the United States. The use of aspirin was considered appropriate when the CVD risk was ≥6% in 10 years and inappropriate when <6%. More than 10% of patients received aspirin inappropriately, but there was a large variability between practices. Interestingly, the patients receiving aspirin inappropriately were 16 years younger than those with appropriate use. Inappropriate use decreased over time, from 15% in 2008 to 9% in 2013. The authors concluded that patients often receive inappropriate aspirin protection for primary prevention and that their findings provide opportunities to improve evidence-based aspirin use for primary prevention.

The study was performed in cardiology practices, in which >70% of the records were missing ≥1 component of the Framingham risk score (6). Because the evidence of aspirin's benefit came from other practices, the results may be biased in that the population seen by cardiologists usually differs from those in general practice.

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TABLE 1 Clinical Setting of 6 Major Randomized Controlled Trials of Aspirin in the Primary Prevention of CVD

Study (Ref. #)	Clinical Setting
British Male Doctor Study (7)	5,139 male U.K. physicians invited from the medical directory
Physicians' Health Study (8)	22,071 male AMA-registered physicians in the United States invited by letter
Thrombosis Prevention Trial (9)	5,499 high-risk male subjects in 108 general group practices in the United Kingdom
HOT (10)	18,790 male and female hypertensive patients in hypertension clinics worldwide
Primary Prevention Project (11)	4,495 male and female subjects in general practices in Italy
Women's Health Study (12)	39,876 female health professionals in the United States

AMA = American Medical Association; CVD = cardiovascular disease; HOT = Hypertension Optimal Treatment.

TABLE 2 5-Year Benefit and Harm of Aspirin in the Primary Prevention of Vascular Disease

	5-Yr Risk of CVD*	Benefit per 1,000	Benefit per 1,000 With Other Prevention†	Harm per 1,000‡	Net Benefit per 1,000§	Net Benefit per 1,000 With Other Prevention
Low	<5%	2	1	1	1	None
Medium	5%–10%	14	8	4	10	4
High	>10%	20	10	10	10	None

*CVD includes cardiovascular death, myocardial infarction, or stroke. †Theoretical situation in which risk is halved by use of statins and other primary prevention measures. ‡Nonfatal gastrointestinal or extracranial bleeding. §Benefit minus harm. Adapted with permission from Baigent et al. (3).

Other abbreviation as in Table 1.

CLINICAL SETTING OF PRIMARY PREVENTION WITH ASPIRIN

The majority of clinical trials that have assessed primary prevention with aspirin were conducted in general practice (i.e., in hypertension clinics) (**Table 1**) (7–12). They did not come from daily cardiology clinic practice. This makes the work of Hira et al. (6) unique and important. Cardiologists mainly see patients with symptomatic heart disease, who are beyond primary prevention, but there may be patients without coronary disease who see a cardiologist for other reasons, such as atypical chest pain, arrhythmia, or heart failure and who are at risk for coronary events. Thus, there is a clear role for the practicing cardiologists in that risk factors should be collected and appropriate prophylactic therapy instituted. However, the basis for the evidence does not initially come from cardiologists.

CONFOUNDING WITH OTHER PREVENTIVE STRATEGIES?

When primary prevention with aspirin is applied, other strategies should be implied as well. There is overwhelming evidence that CVD can be prevented by the use of statins. Although there has never been a randomized trial performed in which the benefit of aspirin relative to statins has been evaluated, it is likely that both are effective given their different modes of action. In fact, observations from randomized trials of statins suggest that these agents potentiate each other (13). Because the bleeding risk of aspirin is strongly related to the ischemic risk, the benefit of aspirin may be overshadowed by the bleeding hazard. Even worse, if aspirin is combined with other strategies that halve the risk of a major ischemic event (e.g., as with statins), aspirin's benefit is almost completed eliminated (theoretically) (**Table 2**), as shown in the meta-analysis discussed earlier (3). In addition, because the cost of statins has dropped dramatically over the years (14), the combination of aspirin with statins has become popular in primary prevention. Therefore, the baseline risk we calculated for the eligibility of aspirin may have changed. In addition to the aforementioned incompleteness of the records, this is another aspect in which the results of the study by Hira et al. (6) may be less applicable in current practice.

Aspirin is effective in the primary prevention of CVD and likely also in cardiology practice. It is associated, however, with excess extracranial bleeding that, regardless of the baseline risk, seems to come close to its benefit. This limitation of aspirin may be due to other preventive strategies currently applied and used extensively in cardiology practice. Thus, inappropriate use of aspirin should be avoided, especially in the younger patient population, as demonstrated in the present study (6).

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